LANDMARK BOOK

Fetal and infant origins of adult disease

Ed D J P Barker.
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Preventive cardiology, epidemiology, and health education have all been particularly concerned with the identification and possible modification of risk factors for cardiovascular diseases among the middle-aged. The recent work of Professor David Barker and his colleagues, which suggests that early life experiences programme the later risk of these diseases, presents a considerable challenge to accepted wisdom, which focuses on adult lifestyle. This book brings together a series of papers, all produced since 1986, which report on the impressive series of studies undertaken by the Southampton group to investigate this hypothesis.

The papers are ordered so as to move from the softer to the harder ends of the spectrum of epidemiological evidence. The weakest evidence came from ecological studies which correlated infant and maternal mortality earlier this century with present day death rates from cardiovascular disease. These analyses corroborated the earlier findings of Forsdahl,[1] that those areas in which infant mortality was high in the past are the ones in which mortality from cardiorespiratory disease is high now. This can be interpreted as demonstrating that the effects of poor living conditions on infant and child development influence susceptibility to disease in adult life. However, as Williams and colleagues pointed out in 1979,[2] areas with high infant mortality earlier this century remain the areas with high infant mortality now, thus the relative importance of factors acting in early life and factors acting in later life cannot be isolated with confidence.[3]

The ecological studies were elaborated to separate correlations of past neonatal and postneonatal mortality with current rates of cardiorespiratory disease mortality. Neonatal mortality—death within 28 days of birth—is taken to be strongly influenced by intrauterine development, while postneonatal mortality—from one to twelve months after birth—is considered to reflect the postnatal environment. Past neonatal mortality rates were most strongly correlated with current stroke death rates, while the areas which now have the highest rates of coronary heart disease and respiratory disease deaths are those which earlier this century had the highest postneonatal mortality rates. This is interpreted as revealing the specific effects on later disease risk of constraint on development at different periods of early growth. An analysis finding strong correlations between past maternal mortality and present stroke mortality provides support for the notion that poor intrauterine development—considered to have occurred most in those areas with high maternal and neonatal mortality—is a particularly important marker for stroke risk.

Elegant though these ecological studies are, they do not rule out the possibility that a combination of the many factors which differ between areas with high and low cardiovascular disease mortality underlies the correlations.[3] To investigate this further, studies based upon individuals rather than areas were initiated. A case-control study which gathered data on childhood environment from patients admitted to hospital with myocardial infarction or stroke, together with controls, produced equivocal findings. The major advance came through the discovery of several sources of data on the early life of individuals now in middle age. These records contained information on placental weight, birth weight, corporal dimensions at the time of birth and measurements of growth during the first year of life. Follow up of these individuals has revealed that poor early growth is related to increased risk of coronary heart disease and respiratory disease mortality; to an increased risk of diabetes and glucose intolerance; to restricted lung function; to raised blood pressure, fibrinogen, and factor VII; and to unfavourable patterning of body fat. Furthermore, specific aspects of suboptimal intrauterine and infant development seem to be related to different endpoints. This is strikingly revealed by the demonstration that it is low birth weight, but *high* placental weight, which is related to raised blood pressure in later life. The suggestion here is that a mismatch between placental weight and birth weight reflects compromised haemodynamic flow during fetal development.

The results of these studies are striking and have already influenced health policy recommendations, as a reading of *The Health of the Nation*[4] makes clear. A few considerations need to be borne in mind before preventive medicine shifts its focus entirely, however. First, the specific hypotheses which are examined have changed as different data sources have become available. Thus the conclusion of a paper exploring the reasons for differentials in mortality between three Lancashire towns was that differences in "postnatal environment, particularly infant feeding, housing, and overcrowding, may be determinants of current differences in adult mortality" (p 68). A later review, however, commented that "research should be directed towards the intrauterine rather than the environment of late childhood—housing, family income, diet, and other influences."[5] Similarly the "moderately complicated"[6] associations between placental weight, birth weight, and later cardiovascular risk factors do not seem to have been postulated before the data were found and analysed.

Second, the key issue of possible confounding by factors acting in later life, but associated with early development, has not been dealt with adequately. Indeed, using data presented for another purpose in one of the papers collected in this book, it was possible to show that smoking in adulthood is related to weight achieved at one year of age.[7] Clearly if such individuals differ in smoking behaviour they are likely to differ in a whole host of other factors which may be causally linked to cardiovascular disease risk. In the introduction, Professor Roger Robinson writes that such studies "at first sight need to cover the whole life span." In reality this is more than an initial appearance: it is not possible to make confident interpretations of the importance of early life factors *unless* potential confounders have been studied.

This was, in fact, well understood earlier this century, when similar notions that later health was determined in infancy and childhood were popular.[8] Leitch, writing in 1951 about work carried out in the 1930s, stated that "Since all the social circumstances, housing, sanitation,

spacing of population and hence exposure to infection, as well as education and, on the whole, facilities for prompt medical attention, improve with, and at about the same rate as, growth, it is difficult to judge whether inhibition of growth itself has any effect on morbidity."[9] The confident assertion in Barker's book that confounding "cannot account for the results of follow up studies of individuals" (p 321) is, at present, going beyond the available evidence. It is, indeed, the ways in which these later influences may operate in different circumstances which need to be considered when the results of those studies which have failed to find associations of the same direction or magnitude as reported by Professor Barker and colleagues are evaluated.[6 10]

Epidemiological studies of cardiovascular disease have often been uninspiring affairs: the work reported in this book provides a corrective to this tendency. Both the strengths and weaknesses of observational epidemiology are illustrated here. Associations of great potential importance can be identified, but making sure that we are not being misled into accepting artefacts as fundamental causes is a more difficult matter.[11] The work of the Southampton group started with the recognition of the unexplained geographical disparities in the risk of cardiovascular disease and the paradoxical finding that such a classic "disease of civilisation" affected the poor more than the rich in contemporary Western societies. Similar paradoxes are generated by the research which followed, however. For example, the studies reported here from the United Kingdom suggest that inhibition of early growth leads to an increased risk of later adult onset diabetes. Yet in Tanzania there are rural communities with severe undernutrition in infancy in which diabetes is rarer than in well nourished Western populations.[12] Uncovering why situations such as this exist may well greatly advance our understanding of the aetiology of some of the most important chronic diseases.

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